General

Guideline Title

Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update.

Bibliographic Source(s)

Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, Goldberg JM, Khatcheressian JL, Leighl NB, Perkins CL, Somlo G, Wade JL, Wozniak AJ, Armitage JO. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2015 Oct 1;33(28):3199-212. [98 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, Bennett CL, Cantor SB, Crawford J, Cross SJ, Demetri G, Desch CE, Pizzo PA, Schiffer CA, Schwartzberg L, Somerfield MR, Somlo G, Wade JC, Wade JL, Winn RJ, Wozniak AJ, Wolff AC. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol. 2006 Jul 1;24(19):3187-205. [128 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

Drug Withdrawal

- January 24, 2008 - WITHDRAWAL: Leukine (sargramostim) : Voluntary market suspension of the current liquid formulation because of an upward trend in spontaneous reports of adverse reactions, including syncope (fainting). The lyophilized form of the drug is not affected. See the U.S. Food and Drug Administration (FDA) Web site for more information.

Recommendations

Major Recommendations

Major Recommendations

Definitions for the rating of evidence (High, Intermediate, Low, Insufficient); types of recommendations (Evidence based, Formal consensus, Informal consensus, No recommendation); and strength of recommendations (Strong, Moderate, Weak) are provided at the end of the "Major Recommendations" field.

Clinical Question 1

In adults treated with chemotherapy for a solid tumor or lymphoma, what factors should clinicians consider when selecting patients for primary prophylaxis of febrile neutropenia with a colony-stimulating factor (CSF)?

Recommendation 1

Primary prophylaxis with a CSF starting in the first cycle and continuing through subsequent cycles of chemotherapy is recommended in patients who have an approximately 20% or higher risk for febrile neutropenia on the basis of patient-, disease-, and treatment-related factors. Primary CSF prophylaxis should also be administered in patients receiving dose-dense chemotherapy when considered appropriate. Consideration should be given to alternative, equally effective, and safe chemotherapy regimens not requiring CSF support when available. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

Clinical Question 2

Among adults treated with chemotherapy for a solid tumor or lymphoma, what factors should clinicians use to select patients for secondary prophylaxis of febrile neutropenia with a CSF?

Recommendation 2

Secondary prophylaxis with CSFs is recommended for patients who experienced a neutropenic complication from a previous cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose or treatment delay may compromise disease free or overall survival (OS) or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

Clinical Question 3

Are there circumstances in which CSFs should be considered for the treatment of neutropenia in adults with cancer?

Recommendation 3.1

Therapy for Patients with Afebrile Neutropenia

CSFs should not be routinely used for patients with neutropenia who are afebrile. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

Recommendation 3.2

Therapy for Febrile Patients with Neutropenia

CSFs should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSFs should be considered in patients with fever and neutropenia who are at high risk for infection-associated complications or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include expected prolonged (>10 days) and profound ($<0.1 \times 10^9$/L) neutropenia, age >65 years, uncontrolled primary disease, pneumonia, hypotension and multiorgan dysfunction (sepsis syndrome), invasive fungal infection, or hospitalization at the time of fever development. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

Clinical Question 4

In what settings should CSFs be used to increase chemotherapy dose density?

Recommendation 4

Dose-dense regimens with CSF support should only be used within an appropriately designed clinical trial or if supported by convincing efficacy data. Efficacy data support the use of CSFs with dose-dense chemotherapy in the adjuvant treatment of high-risk breast cancer and with high–dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (HD-M-VAC) in urothelial cancer. There are limited and conflicting data on the

value of dose-dense regimens with CSF support in non-Hodgkin lymphoma (NHL), and this cannot routinely be recommended at this time. (Type: evidence based, benefits outweigh harms. Evidence quality: high for breast cancer and lymphoma; intermediate for urothelial cancer. Strength of recommendation: strong for breast cancer and lymphoma; moderate for urothelial cancer.)

Clinical Question 5

What is the role of CSFs as adjuncts to progenitor-cell transplantation?

Recommendation 5.1

CSFs may be used alone, after chemotherapy, or in combination with plerixafor to mobilize peripheral-blood progenitor cells. Choice of mobilization strategy depends in part on type of cancer and type of transplantation. (Type: evidence based, benefits outweigh harms. Evidence quality: strong. Strength of recommendation: high.)

Recommendation 5.2

CSFs should be administered after autologous stem-cell transplantation (SCT) to reduce the duration of severe neutropenia. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

Recommendation 5.3

CSFs may be administered after allogeneic SCT to reduce the duration of severe neutropenia. (Type: evidence based. Evidence quality: low. Strength of recommendation: weak.)

Clinical Question 6

What is the role of CSFs in the setting of acute leukemia or myelodysplastic syndromes?

Recommendation 6

The Update Committee did not provide recommendations regarding the use of CSFs in adults with acute myeloid leukemia or myelodysplastic syndromes.

Clinical Question 7

Should CSFs be avoided in patients receiving concomitant chemotherapy and radiation therapy?

Recommendation 7

CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. In the absence of chemotherapy, therapeutic use of CSFs may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected. (Type: evidence based. Evidence quality: high. Strength of recommendation: strong.)

Clinical Question 8

Are there CSF recommendations that apply specifically to older adults and that differ from recommendations in younger adults?

Recommendation 8

Prophylactic CSFs for patients with diffuse aggressive lymphoma age ≥65 years treated with curative chemotherapy (CHOP-R) should be considered, particularly in the presence of comorbidities. (Type: evidence based, benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: moderate.)

Clinical Question 9

How should CSFs be used in the pediatric population?

Recommendation 9.1

The use of CSFs in pediatric patients will almost always be guided by clinical protocols. As in adults, a CSF is reasonable as the primary prophylaxis for pediatric patients with a high likelihood of febrile neutropenia. Similarly, a CSF as secondary prophylaxis or therapy should be limited to high-risk patients. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

Recommendation 9.2

For pediatric indications in which dose-intense chemotherapy is known to have a survival benefit, such as Ewing sarcoma, CSFs should be used to enable the administration of these regimens. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

Recommendation 9.3

CSFs should not be used in pediatric patients with nonrelapsed acute lymphoblastic leukemia (ALL) or nonrelapsed acute myeloid leukemia (AML) who do not have an infection. (Type: informal consensus. Evidence quality: intermediate. Strength of recommendation: moderate.)

Clinical Question 10

What are recommendations for the initiation, duration, dosing, and administration of CSFs?

Recommendations

Recommendations for the administration of filgrastim, tbo-filgrastim, filgrastim-sndz, pegfilgrastim, and sargramostim are summarized in Table 3 in the original guideline document.

Clinical Question 11
Do CSFs differ in efficacy?

Recommendation 11

Pegfilgrastim, filgrastim, tbo-filgrastim, and filgrastim-sndz (and other biosimilars as they become available) can be used for the prevention of treatment-related febrile neutropenia. The choice of agent depends on convenience, cost, and clinical situation. There have been no additional data comparing G-CSF and GM-CSF since the 2006 update; therefore, there has been no change in the recommendation regarding their therapeutic equivalency. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

Clinical Question 12

What is the role of CSFs in the treatment of radiation injury?

Recommendation 12

Current recommendations for the management of patients exposed to lethal doses of total-body radiotherapy, but not doses high enough to lead to certain death as a result of injury to other organs, include the prompt administration of CSFs or pegylated G-CSFs. (Type: formal consensus [by others], benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: moderate.)

Definitions

Guide for Rating Strength of Evidence

Rating for Strength of Evidence	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits versus harms) and that further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction of this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.

Guide for Rating of Potential for Bias

Rating of Potential for Bias	Definitions for Rating Potential for Risk of Bias in Randomized Controlled Trials
Low risk	No major features in the study that risk biased results, and none of the limitations are thought to decrease the validity of the conclusions. The study avoids problems such as failure to apply true randomization, selection of a population unrepresentative of the target patients, high dropout rates, and no intention-to-treat analysis; and key study features are described clearly (including the population, setting, interventions, comparison groups, measurement of outcomes, and reasons for dropouts).
Intermediate	The study is susceptible to some bias, but flaws are not sufficient to invalidate the results. Enough of the items introduce some uncertainty about the validity of the conclusions. The study does not meet all the criteria required for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
High risk	There are significant flaws that imply biases of various types that may invalidate the results. Several of the items introduce serious uncertainty about the validity of the conclusions. The study has serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Guide for Types of Recommendations

Type of Recommendation	Definition
Evidence based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the Expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and reported in the Data Supplement (see the "Availability of Companion Documents" field).
Informal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak").
No recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

Guide for Strength of Recommendations

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.

Weak Rating for Strength of Recommendation	Definition There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

- Cancer (solid tumor and lymphoma)
- Neutropenia and its complications, including febrile neutropenia and infection

Guideline Category

Prevention

Treatment

Clinical Specialty

Oncology

Intended Users

Advanced Practice Nurses

Nurses

Patients

Physician Assistants

Physicians

Guideline Objective(s)

- To update the 2006 American Society of Clinical Oncology guideline on the use of hematopoietic colony-stimulating factors (CSFs)
- To foster the appropriate use of these agents based on high-quality evidence from controlled clinical trials and a comprehensive understanding of the specific patient, disease, and treatment factors associated with the risk of neutropenic complications

Target Population

Adults or children with a solid tumor or lymphoma treated with chemotherapy

Note: The Update Committee did not provide recommendations regarding the use of colony-stimulating factors (CSFs) in adult patients with acute myeloid leukemia or myelodysplastic syndromes.

Interventions and Practices Considered

1. Primary prophylaxis with a colony-stimulating factor (CSF) starting with the first cycle and continuing through subsequent cycles of chemotherapy
2. Secondary prophylaxis with a CSF for patients who experienced a neutropenic complication from a prior cycle of chemotherapy
3. Dose-dense regimens with CSF support
4. CSFs used alone, after chemotherapy, or in combination with plerixafor
5. Administration of CSF after autologous and allogeneic stem-cell transplantation
6. Prophylactic CSFs for patients with diffuse aggressive lymphoma age ≥65 years
7. Use of CSFs in pediatric patients
    - Guided by clinical protocols
    - For indications in which dose-intense chemotherapy is known to have a survival benefit
8. Prompt administration of CSFs or pegylated granulocyte CSFs

Note: The following interventions were considered but not recommended:

- Routine use of CSFs for patients with neutropenia who are afebrile
- Routine use of CSFs as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia
- Use of CSFs in pediatric patients with nonrelapsed acute lymphoblastic leukemia or nonrelapsed acute myeloid leukemia who do not have an infection

Major Outcomes Considered

- Neutropenia- and infection-related outcomes
- Progression-free and overall survival (OS)
- Outcomes related to stem-cell mobilization or transplantation

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Computerized literature searches of MEDLINE and the Cochrane Collaboration Library were performed. The searches of the English-language literature published from October 1, 2005 to September 30, 2014 combined terms for colony-stimulating factors (CSFs), study designs of interest, cancer, and stem cell transplantation. Results of the database searches were supplemented with contributions from Update Committee members' personal files.

Articles were selected for inclusion in the systematic review of the evidence on the basis of the following criteria:

- Population: adults or children with cancer
- Intervention: granulocyte colony-stimulating factors (G-CSFs) and granulocyte macrophage CSFs (GM-CSFs) used to prevent or treat febrile neutropenia among patients treated with chemotherapy, to allow the delivery of dose-dense chemotherapy, to mobilize stem cells for transplantation, or to treat radiation injury

Articles were excluded from the systematic review if they were meeting abstracts not subsequently published in peer-reviewed journals; editorials, commentaries, letters, news articles, case reports, or narrative reviews; or published in a language other than English. Excluded interventions were as follows: topical CSFs, CSFs as immunotherapy or vaccine adjuvant, perioperative CSFs, CSFs in allogeneic donors, CSFs for the prevention of mucositis, and granulocyte transfusion. Also excluded were studies in which the treatment arms received different anticancer drugs.

Outcomes of interest varied by clinical question and included neutropenia- and infection-related outcomes, progression-free and overall survival

(OS), and outcomes related to stem-cell mobilization or transplantation.

For more detailed information on the literature search, see the Methodology Supplement and Data Supplement (see the "Availability of Companion Documents" field).

Number of Source Documents

A total of 66 publications met eligibility criteria and form the evidentiary basis for the guideline recommendations.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Guide for Rating Strength of Evidence

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High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits versus harms) and that further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction of this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.

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Low risk	No major features in the study that risk biased results, and none of the limitations are thought to decrease the validity of the conclusions. The study avoids problems such as failure to apply true randomization, selection of a population unrepresentative of the target patients, high dropout rates, and no intention-to-treat analysis; and key study features are described clearly (including the population, setting, interventions, comparison groups, measurement of outcomes, and reasons for dropouts).
Intermediate	The study is susceptible to some bias, but flaws are not sufficient to invalidate the results. Enough of the items introduce some uncertainty about the validity of the conclusions. The study does not meet all the criteria required for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
High risk	There are significant flaws that imply biases of various types that may invalidate the results. Several of the items introduce serious uncertainty about the validity of the conclusions. The study has serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction

Literature search results were reviewed and deemed appropriate for full text review by one American Society of Clinical Oncology (ASCO) staff reviewer in consultation with the Update Committee Co-chairs. Data were extracted by one staff reviewer and subsequently checked for accuracy through an audit of the data by another ASCO staff member. Disagreements were resolved through discussion and consultation with the Co-Chairs if necessary. Evidence tables are provided in Data Supplements 1 and 2 (see the "Availability of Companion Documents" field).

Study Quality Assessment

Study quality was formally assessed for the randomized controlled trials identified. Design aspects related to the individual study quality were assessed by one reviewer and included factors such as blinding, allocation concealment, placebo control, intention to treat, funding sources, etc. The risk of bias is assessed as "low," "intermediate," or "high" for most of the identified evidence.

For more detailed information on the data analysis, see the Methodology Supplement and Data Supplement (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Panel Composition

The American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines Committee (CPGC) convened an Update Committee with multidisciplinary representation in medical oncology, pediatric oncology, community oncology, epidemiology and biostatistics, patient/advocacy representation, and guideline implementation. The Update Committee was led by two Co-Chairs who had primary responsibility for the development and timely completion of the guideline.

Guideline Development Process

The Update Committee met twice via webinar and corresponded frequently through e-mail. The purpose of the meetings was for members to contribute content, provide critical review, interpret evidence, and finalize the guideline recommendations based upon the consideration of the evidence. All members of the Update Committee participated in the preparation of the draft guideline document, which was then disseminated for external review and submitted to the *Journal of Clinical Oncology (JCO)* for peer review and consideration for publication. All ASCO guidelines are reviewed and approved by the ASCO Clinical Practice Guideline Committee prior to publication.

Development of Recommendations

The guideline recommendations were crafted, in part, using the GuideLines Into DEcision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software™. This method helps guideline panels systematically develop clear, translatable, and implementable recommendations using natural language, based on the evidence and assessment of its quality to increase usability for end users. The process incorporates distilling the actions involved, identifying who will carry them out, to whom, under what circumstances, and clarifying if and how end users can carry out the actions consistently. This process helps the Panel focus the discussion, avoid using unnecessary and/or ambiguous language, and clearly state its intentions.

For more detailed information, see the Methodology Supplement and Data Supplement (see the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

Guide for Types of Recommendations

Type of Recommendation	Definition
Evidence based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
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Informal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak").
No recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

Guide for Strength of Recommendations

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Cost Analysis

Cost Implications

Although the 2006 Update Committee extensively discussed the cost of colony-stimulating factors (CSFs), it recommended CSF use when the febrile neutropenia rate was approximately ≥20% based on clinical impact alone, because of the consensus that reduction in febrile neutropenia itself was an important clinical outcome. Since the 2006 update, original data from randomized trials have been limited.

Cost-effectiveness analyses of primary versus secondary prophylaxis with granulocyte CSFs (G-CSFs) have produced varying results. In a model that considered three different strategies (no primary prophylaxis, 10 days of filgrastim, or one dose of pegfilgrastim) among patients receiving a 21-day cycle of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone (R-CHOP-21) for diffuse large B-cell lymphoma (DLBCL), primary prophylaxis was not cost effective from the perspective of a publicly funded health care system. Costs associated

with no primary prophylaxis, filgrastim prophylaxis, and pegfilgrastim prophylaxis were Canadian $7,314, $13,947, and $16,290, respectively. The incremental cost-effectiveness for primary prophylaxis with filgrastim versus no primary prophylaxis was Canadian $5,796,000 per quality-adjusted life-year, far outside accepted bounds. In a United Kingdom–based model of cost among patients with breast cancer, the most cost effective strategy (primary prophylaxis, secondary prophylaxis, or no G-CSFs) depended on patient characteristics and risk of febrile neutropenia. Of the three types of G-CSFs evaluated, pegfilgrastim seemed to be more cost effective than filgrastim or lenograstim. A cost benefit may be more apparent in the United States, as a result of higher health care costs, but cost effectiveness will vary by factors such as the risk of febrile neutropenia.

Randomized trials have assessed the efficacy of reduced dosages or less frequent administration of prophylactic G-CSFs. A study in the United Kingdom randomly assigned 172 patients with breast cancer to primary prophylaxis with a G-CSF during all six cycles of chemotherapy or during just the first two cycles. Prophylactic G-CSF during only the first two cycles of chemotherapy was cost saving but resulted in a higher rate of febrile neutropenia than a G-CSF during all cycles (36% versus 10%, respectively). A reduced dose of lenograstim (50 μg/body) was evaluated in a small cross-over study of patients with non-Hodgkin lymphoma (NHL) in Japan and compared favorably with a 75-μg/ body dose of filgrastim. In the absence of more definitive data, the consensus of the 2015 Update Committee is that clinicians should adhere to current product labeling.

There do seem to be opportunities to improve G-CSF use in the community. The overuse of CSFs was one of the 2012 Americal Society of Clinical Oncology (ASCO) Choosing Wisely recommendations: "Don't use white cell stimulating factors for primary prevention of febrile neutropenia for patients with less than 20% risk for this complication." To reduce CSF use in patients receiving low-risk chemotherapy regimens, one study group instituted real-time peer-to-peer consultation regarding pegfilgrastim use. Among patients receiving low-risk chemotherapy regimens, pegfilgrastim use decreased from 52 units in the fourth quarter of 2009 to 15 units in the third quarter of 2010 (71% decrease) with no adverse consequences.

Although questions remain about the cost-effectiveness of G-CSFs in certain settings, the 2015 Update Committee has reiterated the position that G-CSF prophylaxis should be driven by clinical considerations and not by cost. CSF use is recommended when the febrile neutropenia rate is ≥20% based on clinical impact alone, because of the consensus that reduction in febrile neutropenia itself is an important clinical outcome. The 2015 Update Committee has recognized, again, that these are expensive agents with the potential for overuse. As stated, when alternative regimens are available that offer equivalent efficacy without the need for CSF support, these alternative regimens should be used.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Members of the Update Committee were responsible for reviewing and approving the final version of the guideline, which was then circulated for external review and submitted to the *Journal of Clinical Oncology* (*JCO*) for editorial review and consideration for publication. All American Society of Clinical Oncology (ASCO) guidelines are ultimately reviewed and approved by the Update Committee and the ASCO Clinical Practice Guidelines Committee before publication.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Hematopoietic colony-stimulating factors (CSFs) have been shown to reduce the duration and severity of neutropenia and the risk of febrile neutropenia and enable delivery of more intensive or dose-dense chemotherapy when indicated.

Potential Harms

- Adverse effects of colony-stimulating factors (CSFs) include bone pain, but a randomized trial of naproxen versus placebo suggested that nonsteroidal anti-inflammatory drugs may reduce the incidence, duration, and severity of bone pain among CSF-treated patients.
- The most common adverse events related to plerixafor were gastrointestinal (GI) disorders and injection site reactions.

Contraindications

Contraindications

Colony-stimulating factors (CSFs) should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum.

Qualifying Statements

Qualifying Statements

- This clinical practice guideline and other guidance published herein are provided by the American Society of Clinical Oncology (ASCO) to assist providers in clinical decision making. The information herein should not be relied on as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Furthermore, the information is not intended to substitute for the independent professional judgment of the treating provider, because the information does not account for individual variation among patients. Recommendations are described as having high, moderate, or low confidence that a recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an as-is basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.
- For adults with a solid tumor or lymphoma who receive chemotherapy regimens that carry a high risk of febrile neutropenia (≥20%), primary prophylaxis substantially reduces the risk of a serious treatment complication and is recommended for most patients. However, for many commonly used chemotherapy regimens, the risk of febrile neutropenia is <20%, and more individualized decisions about colony-stimulating factor (CSF) use are required. The risk of neutropenic complications and the importance of primary prophylaxis will vary with factors such as age, comorbidity, and other treatment-related considerations. It is important that in addition to understanding the evidence-based benefits and other risks of treatment, patients learn about the risk of febrile neutropenia as part of routine chemotherapy education.

Implementation of the Guideline

Description of Implementation Strategy

Guideline Implementation

American Society of Clinical Oncology (ASCO) guidelines are developed for implementation across health settings. Barriers to implementation

include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology* (*JCO*) and *Journal of Oncology Practice*.

For additional information on the ASCO implementation strategy, please see the ASCO Web site.

Implementation Tools

Patient Resources

Quick Reference Guides/Physician Guides

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, Goldberg JM, Khatcheressian JL, Leighl NB, Perkins CL, Somlo G, Wade JL, Wozniak AJ, Armitage JO. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2015 Oct 1;33(28):3199-212. [98 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

1994 Nov (revised 2015 Oct 1)

Guideline Developer(s)

American Society of Clinical Oncology - Medical Specialty Society

Source(s) of Funding

American Society of Clinical Oncology (ASCO)

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2015 Update Committee

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Financial Disclosures/Conflicts of Interest

The Expert Panel was assembled in accordance with the ASCO Conflict of Interest Management Procedures for Clinical Practice Guidelines (summarized at www.asco.org/rwc). Members of the panel completed the American Society of Clinical Oncology (ASCO) disclosure form, which requires disclosure of financial and other interests relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include Employment; Leadership; Stock or Other Ownership; Honoraria, Consulting or Advisory Role; Speaker's Bureau; Research Funding; Patents, Royalties, Other Intellectual Property; Expert Testimony; Travel, Accommodations, Expenses; and Other Relationships. In accordance with these procedures, the majority of the members of the panel did not disclose any such relationships.

Authors' Disclosures of Potential Conflicts of Interest

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I=Immediate Family Member, Inst=My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or http://jco.ascopubs.org/site/ifc .

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Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, Bennett CL, Cantor SB, Crawford J, Cross SJ, Demetri G, Desch CE, Pizzo PA, Schiffer CA, Schwartzberg L, Somerfield MR, Somlo G, Wade JC, Wade JL, Winn RJ, Wozniak AJ, Wolff AC. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol. 2006 Jul 1;24(19):3187-205. [128 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Journal of Clinical Oncology Web site .

Available from American Society of Clinical Oncology, Cancer Policy and Clinical Affairs, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; E-mail: guidelines@asco.org.

Availability of Companion Documents

The following are available:

- Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. Methodology supplement. Alexandria (VA): American Society of Clinical Oncology; 2015. 18 p. Available from the American Society of Clinical Oncology (ASCO) Web site .
- Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. Data supplement. Alexandria (VA): American Society of Clinical Oncology; 2015. 94 p. Available from the ASCO Web site .
- Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. Slide set. Alexandria (VA): American Society of Clinical Oncology; 2015. Available in PDF and PowerPoint formats from the ASCO Web site.
- Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. Summary of recommendations. Alexandria (VA): American Society of Clinical Oncology; 2015. 8 p. Available from the ASCO Web site .

Patient Resources

The following is available:

- White blood cell growth factors. Patient information. 2015 Jul 13. Available from the Cancer.Net Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI on September 1, 1998. It was verified by the guideline developer on December 1, 1998. This summary was updated by ECRI on December 1, 2000, to reflect the information published in the 2000 update of the original guideline (2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. J Clin Oncol 2000 Oct;15[18]:3558-85). The updated information was verified by the guideline developer as of December 20, 2000. This summary was updated by ECRI Institute on July 27, 2006 and on September 2, 2015.

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